

## PATENT COOPERATION TREATY

From the  
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

|                   |       |  |
|-------------------|-------|--|
| To:               | ORDER |  |
|                   | DIARY |  |
| Clyde-Watson, Zoe |       |  |
| D. YOUNG & CO.    |       |  |
| 21 New Finsbury   |       |  |
| London EC4A 1DA   |       |  |
| GRANDE BRASSERIE  |       |  |
| ENTRY             |       |  |
| FOR               |       |  |

SOUTHAMPTON

28 JUL 2004

PCT

NOTIFICATION OF TRANSMITTAL OF  
THE INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT

(PCT Rule 71.1)

Date of mailing  
(day/month/year)

26.07.2004

Applicant's or agent's file reference  
P014594WO ZCW

## IMPORTANT NOTIFICATION

International application No.  
PCT/GB 03/02946International filing date (day/month/year)  
08.07.2003Priority date (day/month/year)  
08.07.2002Applicant  
NOVATHERA LIMITED et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.
2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.
3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.
4. REMINDER

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

The applicant's attention is drawn to Article 33(5), which provides that the criteria of novelty, inventive step and industrial applicability described in Article 33(2) to (4) merely serve the purposes of international preliminary examination and that "any Contracting State may apply additional or different criteria for the purposes of deciding whether, in that State, the claimed inventions is patentable or not" (see also Article 27(5)). Such additional criteria may relate, for example, to exemptions from patentability, requirements for enabling disclosure, clarity and support for the claims.

Name and mailing address of the international  
preliminary examining authority:

European Patent Office  
D-80298 Munich  
Tel. +49 89 2399 - 0 Tx: 523656 apmu d  
Fax: +49 89 2399 - 4465

Authorized Officer

Niedermeyr, G



Tel. +49 89 2399-2939



## PATENT COOPERATION TREATY

## PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT  
(PCT Article 36 and Rule 70)

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                                                          |                                                                                                                                                                |  |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------|--|
| Applicant's or agent's file reference<br>P014594WO ZCW                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                                                          | <b>FOR FURTHER ACTION</b> See Notification of Transmittal of International Preliminary Examination Report (Form PCT/PEA416)                                    |  |
| International application No.<br>PCT/GB 03/02946                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | International filing date (day/month/year)<br>08.07.2003 | Priority date (day/month/year)<br>08.07.2002                                                                                                                   |  |
| International Patent Classification (IPC) or both national classification and IPC<br>G01J3/44                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                                          |                                                                                                                                                                |  |
| Applicant<br>NOVATHERA LIMITED et al.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |                                                          |                                                                                                                                                                |  |
| <p>1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.</p> <p>2. This REPORT consists of a total of 6 sheets, including this cover sheet.</p> <p><input type="checkbox"/> This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).</p> <p>These annexes consist of a total of    sheets.</p> <p>3. This report contains indications relating to the following items:</p> <p>I    <input checked="" type="checkbox"/> Basis of the opinion</p> <p>II   <input type="checkbox"/> Priority</p> <p>III <input type="checkbox"/> Non-establishment of opinion with regard to novelty, inventive step and industrial applicability</p> <p>IV   <input type="checkbox"/> Lack of unity of invention</p> <p>V    <input checked="" type="checkbox"/> Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement</p> <p>VI   <input type="checkbox"/> Certain documents cited</p> <p>VII <input type="checkbox"/> Certain defects in the international application</p> <p>VIII <input type="checkbox"/> Certain observations on the international application</p> |                                                          |                                                                                                                                                                |  |
| Date of submission of the demand<br>06.02.2004                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                                          | Date of completion of this report<br>26.07.2004                                                                                                                |  |
| Name and mailing address of the international preliminary examining authority:<br> European Patent Office<br>D-80298 Munich<br>Tel. +49 89 2399 - 0 Tx: 523656 epmu d<br>Fax: +49 89 2399 - 4465                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                                          | Authorized Officer<br><br>Haller, M<br>Telephone No. +49 89 2399-7042<br> |  |

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT**International application No. **PCT/GB 03/02946****I. Basis of the report**

1. With regard to the **elements** of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17)*):

**Description, Pages**

1-21 as originally filed

**Claims, Numbers**

1-29 as originally filed

**Drawings, Sheets**

1/17-17/17 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT**International application No. **PCT/GB 03/02946**

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

*(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)*

6. Additional observations, if necessary:

**V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

|                               |             |                             |
|-------------------------------|-------------|-----------------------------|
| Novelty (N)                   | Yes: Claims | 12-16, 19, 23-27            |
|                               | No: Claims  | 1-11, 17, 18, 20-22, 28, 29 |
| Inventive step (IS)           | Yes: Claims |                             |
|                               | No: Claims  | 1-29                        |
| Industrial applicability (IA) | Yes: Claims | 1-29                        |
|                               | No: Claims  |                             |

2. Citations and explanations

**see separate sheet**

**INTERNATIONAL PRELIMINARY**

International application No. PCT/GB 03/02946

**EXAMINATION REPORT - SEPARATE SHEET****CITED DOCUMENTS**

Reference is made to the following documents:

- D1: WO 01/51094 A (LIGHTOUCH MEDICAL INC) 19 July 2001 (2001-07-19)  
D2: US 2001/044129 A1 (LING JIAN ET AL) 22 November 2001 (2001-11-22)  
D3: US-B-6 352 5021 (CHAIKEN JOSEPH ET AL) 5 March 2002 (2002-03-05)  
D4: PAPPAS DIMITRI ET AL: "Raman spectroscopy in bioanalysis." TALANTA, vol. 51, no. 1, 24 January 2000 (2000-01-24), pages 131-144, XP001155326 ISSN: 0039-9140  
D5: PUPPELS G J ET AL: "Raman microspectroscopic approach to the study of human granulocytes" BIOPHYSICAL JOURNAL, NOV. 1991, USA, vol. 60, no. 5, pages 1046-1056, XP009017926 ISSN: 0006-3495  
D6: TURYN B ET AL: "Biocompatibility of glass-crystalline materials obtained by the sol-gel method: effect on macrophage function" BIOMATERIALS, ELSEVIER SCIENCE PUBLISHERS BV., BARKING, GB, vol. 17, no. 14, 1 July 1996 (1996-07-01), pages 1379-1386, XP004032709 ISSN: 0142-9612

**Re Item V****Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. The technical field concerned is eliciting and monitoring Raman signals from living cells.
2. **Independent Claims**
  - 2.1. There are two independent claims relating respectively to a method of eliciting a Raman signal (claim 1) and a use of a laser to elicit a Raman signal (claim 28).
  - 2.2. The present application does not meet the criteria of Article 33(1) PCT, because the method of claim 1 is not new in the sense of Article 33(2) PCT.

The documents **D1** and **D2** disclose:

a method of eliciting a Raman signal (**D1**: abstract - **D2**: abstract) from a living cell or a plurality of living cells (**D1**: p. 18, ll. 24-30 - **D2**: abstract) comprising a step of irradiating the cell with a laser having a wavelength of  $785 \pm 60$  nm (**D1**: 785 nm (p. 20, l. 15 - p. 21, l. 31; fig. 1) - **D2**: 780 nm (§

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/GB 03/02946

63)).

- 2.3. Use claim 28 corresponds to independent methods claim 1 and does not disclose any additional features. It is therefore, *mutatis mutandis*, not novel with respect to documents **D1** or **D2** (Art. 33(1), (2) PCT).
- 2.4. It is noted that documents **D3** (col. 2, ll. 48-57; col. 8, l. 22- col. 9, l. 11; fig. 1) and **D4** (§§ 2.2., 3.1 (esp. p. 138, left col., §1), 3.3.) would also take away novelty from at least the independent claims 1 and 28.

**3. Dependent Claims****3.1. Dependent claims 2-11, 17, 18, 20-22 and 29**

Dependent claims 2-11, 17, 18, 20-22 and 29 are not new as documents **D1**, **D2**, **D3** and/or **D4** disclose:

- |                 |                                                                                                                                                                                               |
|-----------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| cls. 2, 29:     | see § 2.2 above.                                                                                                                                                                              |
| cls. 3-6:       | 4 successive 400 second measurements ( <b>D1</b> : p. 25, ll. 13-24) at a power of between 300 to 700 mW ( <b>D1</b> : p. 21, ll. 1-4) yielding a total energy of between 480 to 1120 Joules  |
| cls. 7, 8:      | irradiation of the cell at intensities of 50-300 mW ( <b>D3</b> : col. 8, l. 66- col. 9, l. 11)                                                                                               |
| cl. 9:          | an irradiation period of "up to 40 minutes" (i.e. 40 minutes or less - <b>D1</b> : p. 25, ll. 13-24)                                                                                          |
| cls. 10, 11:    | focussing of the laser within the nucleus or cytoplasm ( <b>D2</b> : § 38)                                                                                                                    |
| cl. 17, 20:     | measuring changes in a cell - induced by a pharmaceutical agent - by measuring changes in the Raman signal over a period of time ( <b>D2</b> : §§ 35-46; <b>D4</b> : p. 140, right col., § 2) |
| cl. 18, 21, 22: | detecting changes in phenotype, protein or DNA/RNA levels (e.g. <b>D1</b> , (p. 25, ll. 9-12; <b>D3</b> : col. 14, ll. 19-23; col. 14, l. 61-col. 15, l. 1)                                   |

**3.2. Dependent claims 12-16, 19 and 23-27**

Dependent claims 12-16, 19 and 23-27 do not contain any features which, in combination with the features of any claim to which they refer, meet the requirements of the PCT in respect of inventive step (Article 33(3) PCT), the reasons being as follows:

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/GB 03/02946

- cls. 13-16: The different cell culturing substrates disclosed can be considered to constitute straightforward possibilities from which the skilled person would select, in accordance with circumstances, without the exercise of inventive skill - see, for instance, document **D5** (p. 1047, left col., § 3; **D6** (abstract))
- cls. 12, 23: Recording Raman spectra from the extracellular matrix comes within the scope of the customary practice followed by persons skilled in the art, seeking - for instance - to subtract the background signal.
- cls. 19, 24-27: The selection of a whole range of possible applications for Raman spectroscopy would be obvious to the person skilled in the art.